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(71) Applicant: UNIVERSITY OF FLORIDA [US/US]; 223 Grinter Hall, Gainesville, FL 32611 (US).

(72) Inventors: BAZER, Fuller, W. ; 4410 N.W. 20th Place, Gainesville, FL 32605 (US). JOHNSON, Howard, M. ; 4404 N.W. 75th Street, Gainesville, FL 32606 (US).

(74) Agents: SALIWANCHIK, David, R. et al.; Saliwanchik & Saliwanchik, 2421 N.W. 41st Street, Suite A-1, Gainesville, FL 32606 (US).

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(54) Title: COMPOSITION FOR THE INHIBITION OF TUMORS AND FOR THE NON-CYTOTOXIC INHIBITION OF REPLICATION OF VIRUSES

(57) Abstract

Use of ovine trophoblast protein-1 (-OTP-1) or fragments thereof to inhibit viral activity and tumor formation and growth. OTP-1 exhibits potent antiviral activity but, advantageously, does not have cytotoxic effects.

DESCRIPTION

COMPOSITION FOR THE INHIBITION OF TUMORS AND FOR THE NON-CYTOTOXIC INHIBITION OF REPLICATION OF VIRUSES

Background of the Invention

Viruses are known to be responsible for a large number of disease conditions in humans and animals. Viruses have been implicated in disorders ranging from the flu to cancer. Recently, RNA viruses have been associated with Acquired Immune Deficiency Syndrome (AIDS) and AIDS Related Complex (ARC).

AIDS and ARC are major worldwide health problems which have received a great deal of attention. AIDS is notorious not only for its rapid spread but also for the high percentage of deaths among those who contract the disease. Although enormous sums of money and hours of manpower have been invested in an attempt to understand this disease, therapies and prophylactic compositions have proven to be extremely elusive.

The research on AIDS has led to the identification of the causative agent and to a generalized knowledge of how the disease occurs. It is now known that retrovirus infections are responsible for AIDS and ARC. Specifically, the viruses responsible for these conditions are referred to as human immunodeficiency viruses (HIV).

Unfortunately, the prevention and treatment of HIV infections is extremely difficult for a number of reasons including the existence of a variety of strains, and the mechanism whereby the virus replicates within cells of the host. AIDS is extremely problematic to treat because it is difficult to inactivate the retrovirus without producing toxic side effects in the host.

For example, AZT which apparently has some ability to inhibit the AIDS virus can be very toxic to the host. Other antivirals, including interferons, also may have hazardous side effects. Therefore, a critical need exists to identify compounds with potent antiviral properties but which do not have toxic side effects on humans or other host animals.

Antiviral agents have been isolated from an extremely wide variety of sources. The compounds of the subject invention are involved in the reproductive biochemistry of mammals.

It has been established that the conceptus membranes or trophectoderm of various mammals produces biochemical signals that allow for the establishment and maintenance of pregnancy (Bazer, F.W., and First, N.L. [1983] J. Animal Sci. 57, Sup. 2:425-459). It was established in 1979 that sheep conceptuses secrete a low molecular weight protein on day 16 of gestation (Wilson, Lewis and Bazer [1979] Biology of Reproduction 20, Sup. 1:101A, Abstract). Later, this protein was shown to be secreted by sheep conceptuses between days 10 and 21 of pregnancy (Bazer et al. [1986] J. Reproduction and Fertility 76:841-850); therefore, it was named ovine trophoblast protein-one (oTP-1). oTP-1 was shown to have antiluteolytic biological activity since it inhibited uterine secretion of prostaglandin F_2-alpha which causes the corpus luteum on the ovary to undergo physiological and endocrinological demise in nonpregnant sheep (Bazer et al. [1986]). The primary role of oTP-1 was assumed to be associated with the establishment of pregnancy.

Subsequently, it was found that oTP-1 has some structural similarity to interferons of the alpha class. The highest amino acid sequence homology is to bovine interferon alpha II (Imakawa et al. [1987] Nature 330:377-379; Stewart et al. [1987] J. Endocrin. 115:R13-R15). However, other interferons are not known to have any role in the biochemical regulation of reproductive cycles.

The therapeutic usefulness of alpha interferons in the treatment of various types of cancer is well established. Alpha interferons are especially useful against hematologic malignancies such as hairy-cell leukemia (Quesada, J.R., Reuben, J., Manning, J.T., Hersh, E.M., and Gutterman, J.U. [1984] New England Journal of Medicine 310:15). Alpha interferons have also shown substantial antitumor activity against multiple myeloma, chronic lymphocytic leukemia, low-grade lymphoma, Kaposi's sarcoma, chronic myelogenous leukemia, renal-cell carcinoma, urinary bladder tumors and ovarian cancers (Bonnem, E.M., and Spiegel, R.J. [1984] J. Bio. Response Modifiers 3:580; Oldham, R.K. [1985] Hospital Practice, Dec. 15, p. 17).

Significantly, however, the usefulness of alpha interferons is limited by their toxicity.

Brief Summary of the Invention

The subject invention concerns the novel use of proteins secreted by the conceptuses of various animals to inhibit tumor formation, viral activity, and retrovirus activity. Although these compounds have certain structural similarities to alpha interferons, the proteins of the subject invention are highly advantageous because they exert their inhibitory effect on viruses, retroviruses, and tumors without harming the cells of the host animal or otherwise producing hazardous side effects. This surprising lack of cytotoxicity makes these compounds excellent for use in the treatment of cancers, viral diseases, and retroviral diseases such as acquired immunodeficiency syndrome. Also, the proteins of the subject invention were found to have unexpectedly high antiviral activity. Compared to other interferon-type proteins, the proteins of the subject invention have similar antiviral effects.

The proteins of the subject invention can be purified from a variety of animal conceptuses including sheep, pigs, horses, cattle, and humans. The

proteins may also be produced by recombinant means. Therapeutic compositions containing the proteins may be administered systemically or, in the case of tumors, local administration may be preferred.

Brief Description of the Drawing

Figure 1 is the predicted amino acid sequence of oTP-1.

Detailed Description of the Invention

Ovine trophoblast protein-1 (oTP-1) is an antiluteolytic protein which plays an important role in maternal recognition of pregnancy. oTP-1 is purified from medium in which sheep conceptuses have been cultured. Purity of the oTP-1 is based on the presence of a single band of protein following one-dimensional polyacrylamide gel electrophoresis and staining of the gel with silver and by radiochemically demonstrating a single protein radiolabeled with ^{125}I (Pontzer et al. [1988]).

We show here that purified oTP-1 has high specific antiviral activity and is thus as potent as any known interferon (IFN). It has been determined that oTP-1 has antiviral activity of about 200 million units of antiviral activity per milligram of highly purified oTP-1 (Pontzer et al. [1988] Biochem. Biohphys. Res. Comm. 152:801-807). oTP-1 is, structurally, antigenically, and functionally distinct from both ovine and bovine IFN-alphas. The antiviral activity of oTP-1 was found to exist in Day 12 through Day 16 conceptus culture medium and in allantoic fluid from Day 60 of pregnancy.

A particularly attractive feature of the compounds of the subject invention is the lack of any evidence of toxicity. This is not the case for the currently used alpha IFNs in tissue culture or for in vivo treatment of cancer and viral diseases. Thus oTP-1 and related proteins from other species should be effective and unique biologicals for use in cancer therapy.

Unless otherwise indicated, the term "virus," as used here, refers to both DNA and RNA viruses.

Materials and Methods

Reagents. Conceptuses can be collected from pregnant sheep and cultured in vitro in a modified Minimum Essential Medium as described previously (Godkin, J.D., F.W. Bazer, J. Moffatt, F. Sessions, and R.M. Roberts [1982] J. Reprod. Fert. 65:141-150). Conceptuses can be collected on various days of the estrous cycle with the first day of the cycle being designated as Day 0. oTP-1 can be purified from conceptus culture medium as described by Vallet et al. (Vallet, J.L., F.W. Bazer, and R.M. Roberts [1987] Biol. Reprod. 37:1307-1316). The homogeneity of oTP-1 can be assessed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Protein determinations on purified oTP-1 can be performed using the bicinchoninic (BCA) assay (Pierce Chemical Co., Rockford, IL) (Smith, P.K., R.I. Krohn, G.T. Hermanson, A.K. Mallia, F.H. Gartner, M.D. Provenzano, E.K. Fujimoto, N.M. Goeke, B.J. Olson, and D.C. Klenck [1985] Anal. Biochem. 150:76-85).

Recombinant bovine IFN-alpha (rBoIFN-alpha) and rBoIFN-gamma were obtained from Genentech Incorporated (South San Francisco, CA). The reference preparation of recombinant human IFN-alpha (rHuIFN-alpha) is available from the National Institutes of Health, and commercial rHuIFN-alpha can be purchased from Lee Biomolecular (San Diego, CA). The production of ovine interferons can be induced in ovine peripheral blood leukocytes by a 3 day incubation with staphylococcal enterotoxin A (for IFN-gamma), or a 24 hour infectivity with Newcastle disease virus (for IFN-alpha). Polyclonal antisera to oTP-1 or rBoIFNs can be produced by hyperimmunization of rabbits.

All tissue culture media, sera and IFNs used in this study were negative for endotoxin, as determined by assay with Limulus amebocyte lysate (Associates of Cape Cod, Woods Hole, MA) at a sensitivity level of 0.07 ng/ml.

Following are examples which illustrate procedures, including the best mode, for practicing the invention. These examples should not be construed as

limiting.

All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1 - Antiviral Activity of oTP-1

The relative specific activity of oTP-1, purified to homogeneity, was evaluated in antiviral assays to ascertain whether oTP-1 could be classified appropriately as an interferon. Although within the same range, oTP-1 had a higher specific activity than either rBoIFN-alpha or rBoIFN-gamma (Table 1). The NIH standard preparation of rHuIFN-alpha had a similar specific activity, while a commercial preparation of rHuIFN-alpha exhibited lower specific antiviral activity. Comparable relative activity was demonstrated using either bovine or ovine cells.

Table 1. Antiviral Activity of oTP-1 and known IFNs.

	Specific Activities*	
	MDBK	Shnf
oTP-1	2×10^8	3×10^8
rBoIFN-alpha	6×10^7	1×10^7
rBoIFN-gamma	4.5×10^6	3×10^6
NIH rHuIFN-alpha	2.2×10^8	2.2×10^8
rHuIFN-alpha	2.9×10^5	4.3×10^5

*Specific activities are expressed in units IFN/mg protein obtained from antiviral assays using either Madin Darby bovine kidney (MDBK) cells or sheep normal fibroblasts (Shnf). All samples were assayed simultaneously so as to eliminate interassay variability. Results represent the mean of four determinations where the standard deviation was less than 10% of the mean.

Example 2 - Reproductive Functions of oTP-1

Although oTP-1 is a member of the IFN-alpha family based on structure and its potent antiviral properties, the IFN-alphas studied to date do not possess the potent reproductive properties associated with oTP-1. We have recently found, for example, that uterine lumen infusion of ewes with oTP-1 extends the corpus luteum life span as assessed by interestrous intervals, maintenance of progesterone secretion, and inhibition of prostaglandin secretion. Recombinant human IFN-alpha$_2$ at similar concentrations had no effect. Also, recombinant bovine IFN-gamma has little or no effect on interestrous interval compared to oTP-1 (Table 2).

Table 2. Effect of Interferons on Reproductive Physiology

Treatment	Interestrous Interval
Control	16.8 days
rBoIFN-alpha	
200 ug/day	16.0 days
2000 ug/day	19.3 days
oTP-1	
100 ug/day	27.0 days

Therefore, although oTP-1 has some similarities to other interferons, it has very distinctive properties of its own. Despite sequence homology between oTP-1 and other interferons, no other interferon is known to have the capability of significantly influencing the biochemical events of the estrous cycle.

Example 3 - Additional Distinguishing Features of oTP-1

We have synthesized two peptides corresponding to the N-terminal 37 amino acids, oTP-1 (1-37), and the highly hydrophilic C-terminal 34-mer, oTP-1 (139-172). oTP-1 (1-37) contains a large segment of the predicted first loop region as well as ß-turn (25-29). Both the N- and C-terminal oTP-1 peptides blocked oTP-1 antiviral activity on MDBK cells with the C-terminal peptide having greater efficacy. The N-terminal peptide had no effect on the antiviral activity of natural ovine IFN-alpha, rBoIFN-alpha, or rBoIFN-gamma, while the C-terminal peptide blocked the antiviral activity of both IFN-alphas, but had no effect on IFN-gamma. Clearly, therefore, oTP-1 is immunologically distinguishable from these other interferons. An irrelevant peptide of similar size (33-mer) corresponding to the N-terminal extracellular arm of the mouse ß-adrenergic receptor did not diminish oTP-1 antiviral activity.

Thus, the inhibition of IFN function by the synthetic peptides appears to be specific. The peptides displayed no evidence of toxicity when added to cells in the absence of virus. Similar results have been obtained using the human WISH cell line. The blockage of oTP-1 antiviral activity suggests that oTP-1 and the IFN-alphas bind to the same site on the receptor at the C-terminal end of the molecule. The fact that the N-terminal peptide only inhibited oTP-1 function, could indicate that this region of the molecule is responsible for its unique properties (low toxicity for example).

Example 4 - Occurrence of oTP-1 at Various Stages of the Reproductive Cycle

Characterization of the antiviral activity of oTP-1 was extended to examination of additional sources of oTP-1. Conceptus cultures from Day 12 through Day 16 had increasing antiviral activity associated with advancing development of the conceptus (Table 3). That this in vitro antiviral activity could

have physiologic relevance was substantiated by demonstration of antiviral activity of the same magnitude, 7.3 x 10^5 units/ml with a range of from 3 x 10^5 to 3 x 10^6, in the 20 ml uterine flushings from Day 16 pregnant ewes.

Antiviral activity attributable to oTP-1 could be detected later in pregnancy. Allantoic fluid from Day 60 had substantial antiviral activity (Table 3). The source of oTP-1 in the allantoic fluid is most likely the chorion, since it developed from the trophectoderm which is initially responsible for oTP-1 secretion by sheep conceptuses. Low levels of antiviral activity present at the same time in amniotic fluid may be accounted for by movement from the allantois. Detectable levels of antiviral activity remained in the allantoic fluid at Day 100, but had diminished to essentially undetectable levels by Day 140 in both amniotic and allantoic fluids.

Confirmation of oTP-1 as the antiviral agent in these fluids was provided by the ability of antisera to oTP-1 to specifically block that activity, while antisera to rBoIFN-alpha was without effect. The antisera to rBoIFN-alpha are known to react with ovine IFN-alpha. The antiviral activity of oTP-1 could, therefore, be demonstrated late as well as early in pregnancy with potentially different functions at different times. While the antiluteolytic effect is essential early in pregnancy, the antiproliferative and immunosuppressive effects of IFNs in addition to their antiviral activity could be most significant later in pregnancy.

Table 3. oTP-1 antiviral activity in conceptus cultures and allantoic and amniotic fluids.*

	Day	Samples	Units/ml
Conceptus cultures:			
	10	9	<3
	12	5	34
	13	6	4.5×10^3
	14	3	7.7×10^3
	16	12	2.0×10^6
Allantoic fluid:			
	60	3	1.4×10^3
	100	4	11
	140	3	<3
Amniotic fluid:			
	60	3	22
	100	4	<3

*Antiviral activity was assessed on Madin Darby bovine kidney cells. A minimum of three samples was examined at each time point, and each was assayed in triplicate. Results are expressed as mean units/ml.

Example 5 - Anti-retroviral Activity and Cytotoxic Effects of oTP-1

Highly purified oTP-1 was tested for anti-retroviral and cytotoxic effects on peripheral blood lymphocytes exposed to the feline AIDS retrovirus. This lentivirus produces a chronic AIDS-like syndrome in cats and is a model for human AIDS (Pederson et al. [1987] Science 235:790-793). Replication of the virus in peripheral blood lymphocytes is monitored by reverse transcriptase activity in culture supernatants over time.

Addition of oTP-1 produced a rapid, dose-dependent decrease in reverse transcriptase (RT) activity (Table 4). While concentrations as low as 0.62 ng/ml of oTP-1 inhibited viral replication, much higher concentrations (>8000 units/ml)

with concurrently greater effects were without toxic effects on the cells. It was determined that replication of the feline immunodeficiency virus was reduced very significantly compared to control values when cells were cultured in the presence of oTP-1.

Table 4. Effect of oTP-1 on FIV Replication

oTP-1 Concentration (ng/ml)	RT Activity (cpm/ml)				
EXPERIMENT 1					
	Harvest Days				
	Day 2	Day 5	Day 8	Day 12	Day 15
0.00	93,908	363,042	289,874	171,185	125,400
0.62	77,243	179,842	172,100	218,281	73,039
1.25	94,587	101,873	122,216	71,916	50,038
2.50	63,676	72,320	140,783	75,001	36,105
5.00	69,348	82,928	90,737	49,546	36,299
EXPERIMENT 2					
	Harvest Days				
	Day 2	Day 5	Day 8	Day 13	Day 17
0.0	210,569	305,048	279,556	500,634	611,542
2.5	121,082	106,815	108,882	201,676	195,356
5.0	223,975	185,579	108,114	175,196	173,881
10.0	167,425	113,631	125,131	131,649	129,364
20.0	204,879	80,399	59,458	78,277	72,179
40.0	133,768	54,905	31,606	72,580	53,493

It is especially significant that oTP-1 exerted no cytotoxic effect on the host cells of the retrovirus. This was true even when oTP-1 was present at 40 ng per ml of culture medium which is equivalent to about 8,000 antiviral units of alpha interferon when oTP-1 is assayed for its ability to protect madin darby bovine kidney cells from lysis by vesicular stomatitis virus as described by Pontzer et al. (1988). Thus, the antiviral activity of oTP-1 or its equivalent from animals may have broad therapeutic applications without the toxic effects usually associated with high dose treatment with IFN-alphas.

Although the presence of oTP-1 in culture medium inhibited reverse transcriptase activity of the feline immunodeficiency virus, this is not due to a direct effect of oTP-1 on the FIV. Rather, oTP-1, like other IFNs, appears to induce the host cell to produce a factor(s) which is inhibitory to the reverse transcriptase of the virus.

Example 6 - Effect of oTP-1 on HIV Infected Human Peripheral Lymphocytes

oTP-1 has also been tested for activity against HIV infection of human cells. Human peripheral lymphocytes which had been infected with HIV were treated with varying concentrations of oTP-1. As shown in Table 5, concentrations of oTP-1 produced very significant antiviral effects. A concentration of only 10 ng/ml resulted in over a 50% reduction in RT activity after only six days. 500 ng/ml resulted in a 90% reduction in RT activity within 10 days.

Table 5. Effect of oTP-1 on HIV Replication in Human Peripheral Lymphocytes

oTP-1 Concentration (ng/ml)	RT Activity			
	Day 6		Day 10	
	cpm/ml	% reduction	cpm/ml	% reduction
0	4,214	--	25,994	--
10	2,046	51	9,883	62
50	1,794	57	4,962	81
100	1,770	58	3,012	88
500	1,686	60	2,670	90
1000	1,499	64	2,971	89

oTP-1 was found to exert its remarkable antiviral activity without adverse effects on the cells. Table 6 shows that no evidence of cytotoxic effects attributable to the administration of oTP-1 has been observed.

Table 6. Effect of oTP-1 on Viability of HIV Infected Human Peripheral Lymphocytes

oTP-1 Concentration (ng/ml)	Viable Cells/ml x 10^5		
	Day 3	Day 6	Day 13
0	16.0	7.5	5.3
10	13.0	7.5	6.0
50	13.0	11.5	9.0
100	15.0	8.5	9.5
500	16.5	12.0	11.0
1000	21.9	9.5	8.5

Example 7 - Synthetic Fragments of oTP-1

The amino acid sequence of oTP-1 has been predicted from the cDNA (Figure 1). Using this sequence, a surface profile for oTP-1 has been derived taking into account: (a) HPLC hydrophilicity parameters; (b) accessibility parameters; and (c) segmental mobility. Those regions which are expected to have functional activity are a long stretch of residues in the amino terminus from approximately 18-53, in addition to 68-76, 88-114, 130-138, and the carboxy terminal 14 amino acids.

Secondary structure predictions have also been made based on the amino acid sequence. The protein is expected to be generally globular with protruding unstructured loops and ß-turns. The loop/bend regions coincide with segments predicted to be on the surface of the molecule by the composite profile. Therefore, nonconserved regions of secondary structure may serve to stabilize oTP-1 with the ß-turns being responsible for the elicitation of various functions.

Example 8 - Other Conceptus-Derived Interferons

Proteins secreted by conceptuses of other species show some similarity to oTP-1. These proteins also should have high antiviral activity with minimal cytotoxic effects. Therefore, interferons produced by conceptuses of each species offer unique therapeutic agents for the control of retroviruses and cancers.

As used here, the term "conceptus-derived interferon" refers to compounds having a molecular weight between about 15,000 and about 30,000 daltons, having antiviral activity, and which are secreted by the conceptus, or are otherwise present in conceptus cultures, or can be derived from proteins present in conceptus cultures.

Conceptus-derived interferons can be obtained from a variety of animals using the same general procedures as those which are used to obtain oTP-1. For

example conceptuses can be obtained from horses, cows, pigs, rabbits, rats, mice, or humans and cultured in vitro in a modified Minimum Essential Medium as described in Godkin et al. (1982). Interferons can be purified from the conceptus culture medium as described by Vallet et al. (1987). Necessary modifications to these procedures will be readily apparent to those skilled in the art. As with other proteins, the proteins of interest here can be analyzed and assessed for homogeneity by SDS-PAGE.

The antiviral properties of the isolated conceptus-derived proteins can then be ascertained using the assays described in the examples above.

Example 9 - Inhibition of Cellular Growth

oTP-1 or other conceptus-derived proteins may also be used to inhibit cellular growth. Thus, formulations comprising the compounds of the subject invention can be used to inhibit, prevent, or slow tumor growth. Suitable formulation for antitumor and antiviral applications are described in Example 10.

Example 10 - Pharmaceutical Compositions

oTP-1 and the other compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations comprising interferons or interferon-like compounds have been described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, Remington's Pharmaceutical Science by E.W. Martin describes formulations which can be used in connection with the subject invention. In general, the compositions of the subject invention will be formulated such that an effective amount of the conceptus-derived interferon is combined with a suitable carrier in order to facilitate effective administration of the composition.

The compounds of the subject invention can be parenterally, orally, or topically administered to subjects requiring antitumor or antiviral treatment. The active compounds may be mixed with physiologically acceptable fluids such as saline or balanced salt solutions. Also, solid formulations such as tablets or capsules can be made.

Dosage rates, in terms of units applied daily, may parallel dosage rates commonly used for such treatments. For example, the dosage range may be from about 10^5 to 10^8 units daily. Because of the very potent antiviral activity of the compounds of the subject invention, the quantity of active material administered may be less than that required for other interferon compositions. Also, because of the low toxicity of the conceptus-derived compounds, higher dosages may be administered. For long term administration, low dosages may be desired while higher dosages may be administered for some short term treatments.

The compounds of the subject invention may be applied, for example, orally, intravenously, intramuscularly, intraperitoneally, intranasally, intradermally, or subcutaneously. The compounds of the subject invention may also be combined with other antiviral or tumor inhibiting substances to provide an enhanced treatment.

Claims

1. A method for inhibiting tumor growth which comprises treatment with an effective amount of a conceptus-derived interferon.

2. A method, according to claim 1, wherein said interferon is obtained from a mammal.

3. A method, according to claim 2, wherein said mammal is selected from the group consisting of horses, cows, sheep, pigs, rabbits, rats, mice, and humans.

4. A method, according to claim 1, wherein said interferon is oTP-1 or an immunologically equivalent variant or fragment thereof.

5. A method, according to claim 1, wherein said treatment comprises the administration of an effective amount of an interferon having the same, or an equivalent, amino acid sequence as that which is shown in Figure 1.

6. A method for inhibiting, controlling, or preventing viral or retroviral replication, said method comprising treatment with an effective amount of a conceptus-derived interferon.

7. A method, according to claim 6, wherein said interferon is obtained from a mammal.

8. A method, according to claim 7, wherein said mammal is selected from the group consisting of horses, cows, sheep, pigs, rabbits, rats, mice, and humans.

9. A method, according to claim 6, wherein said interferon is oTP-1 or an immunologically equivalent variant or fragment thereof.

10. A method, according to claim 6, wherein said treatment comprises the administration of an effective amount of an interferon having the same, or an equivalent, amino acid sequence as that which is shown in Figure 1.

11. A method, according to claim 6, wherein said retrovirus is selected from the group consisting of HIV and FIV.

12. A composition for inhibiting tumor growth or viral replication, said composition comprising an effective amount of a conceptus-derived interferon and a pharmaceutically acceptable carrier or diluent.

13. A composition, according to claim 12, wherein said interferon is obtained from a mammal.

14. A composition, according to claim 13, wherein said mammal is selected from the group consisting of horses, cows, sheep, pigs, rabbits, rats, mice, and humans.

15. A composition, according to claim 12, wherein said interferon is oTP-1 or an immunologically equivalent variant or fragment thereof.

16. A peptide selected from the group consisting of the following peptides and immunologically equivalent variants: residues 18 through 53, residues 68 through 76, residues 88 through 114, residues 130 through 138, and the carboxy terminal 14 amino acids.